Urinary podocytes: Lost and found alive

The glomerular podocyte is a terminally differentiated cell that lines the outer aspect of the glomerular basement membrane (GBM). It, therefore, forms the final barrier to protein loss, which explains why podocyte injury is typically associated with marked proteinuria. Indeed, all forms of nephrotic syndrome are characterized by abnormalities in the podocyte [1]. Podocytes are injured in many forms of human and experimental glomerular disease, including minimal change disease, focal segmental glomerulosclerosis, membranous glomerulopathy, diabetes mellitus, and lupus nephritis [1]. Independent of the underlying disease, the early events are characterized by molecular alterations of the slit diaphragm without visible morphologic changes or, more obviously, by a reorganization of the foot process structure with fusion of filtration slits and apical displacement of the SD [1].

From the standpoint of progressive glomerular disease, it is important to recognize that if the early structural changes are not reversed, severe and progressive glomerular damage develops [2]. This involves podocyte vacuolization, pseudocyst formation, and detachment of podocytes from the GBM, resulting in podocyte depletion. These events underlie the formation of synchiae via attachment of parietal epithelial cells of Bowman’s capsule to denuded GBM areas [2]. These changes are irreversible and ultimately lead to the development of glomerulosclerosis and end-stage renal failure [2]. Studies in human diabetic nephropathy [3–5], in the chronic puromycin model of glomerulosclerosis [6], and transforming growth factor-β1 transgenic mice [7] collectively provided convincing evidence for a correlation between the loss of podocyte and the progression of glomerular diseases.

The detection of urinary podocytes does not come as a surprise. In fact, several studies have previously documented the presence of urinary podocytes in a variety of experimental and human glomerular diseases [8–17]. However, the viability of these cells was not determined. More importantly, the cellular origin of these cells was not entirely clear because these earlier studies relied on the identification of podocytes as podocalyxin-positive cells. This, however, is not sufficient to characterize the cells as podocytes, because podocalyxin is widely expressed by other cells, including vascular endothelial cells and platelets, and hematopoietic stem cells [18–20].

More recently Vogelmann et al [21] reported the urinary excretion of viable human podocytes in health and renal disease and concluded that in active disease, viable podocytes detach from the glomerular tuft due to local environmental factors, rather than defects in the podocytes, per se, whereas in healthy individuals mostly senescent podocytes are shed.

The paper by Petermann et al [22] in this issue of Kidney International takes the story a step further in that it not only analyzes the identity and viability of urinary podocytes, but also correlated it with the podocyte number in the kidneys from which these podocytes had been shed. In addition, they analyzed the proliferative capacity of the podocytes after they lost their connection with the GBM. Urinary cells that had been harvested from rats with experimental membranous nephropathy were positive for a large variety of podocyte-specific markers, including synaptopodin, nephrin, podocin, WT-1, and GLEPP1. Another major finding of this study was the fact that the urinary podocytes showed an initial proliferation during the first 5 days of in vitro culture. This proliferative wave was then followed by dramatic apoptosis leading to a net loss of cultured urinary podocytes. Taken together, these results show that detached podocytes are not only viable but also have retained or regained a limited proliferative capacity [22].

So what do we learn from these studies? The finding that urinary podocytes shed from glomeruli of diseased rats can undergo cell division before they ultimately undergo apoptosis has several implications. Most excitingly, these studies shed new light on the dual role of the GBM and/or the podocyte-GBM adhesion/signaling system. The data by Petermann et al implies that the GBM provides signals that suppress both podocyte proliferation and apoptosis. This idea is in line with novel results form Huber et al [23], who showed that CD2AP null podocytes are more susceptible to detachment-induced cell death than wild-type podocytes. These results suggest that when podocytes are no longer adherent to the GBM in vivo, they regain the capacity to proliferate, but this comes at the price of increased cell death. It would be interesting to see whether the cultivation of the urinary podocytes on isolated GBM preparations can prevent the apoptosis.

In summary, the present study by Petermann et al established that adult podocytes retain or regain a certain potential for replication and may, therefore, be not terminally differentiated as generally assumed. These data raise the intriguing possibility that it should be possible in the future to establish conditions under which podocytes

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may transiently proliferate in vivo. This would eventually allow the restoration of the normal podocyte number in diseases with progressive podocyte loss, thereby preventing the progression to ESRD. Clearly, there is a long way to go, but the paper by Petermann et al represents an important first step in this direction.

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REFERENCES